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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/758,335	01/15/2004	Seth J. Orlow	71369.368 and PFI-016CIPD	6410

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EXAMINER	
ANDERSON, JAMES D	
ART UNIT	**PAPER NUMBER**
1614	

SHORTENED STATUTORY PERIOD OF RESPONSE	NOTIFICATION DATE	DELIVERY MODE
3 MONTHS	01/22/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Notice of this Office communication was sent electronically on the above-indicated "Notification Date" and has a shortened statutory period for reply of 3 MONTHS from 01/22/2007.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/758,335	ORLOW ET AL.	
	Examiner	Art Unit	
	James D. Anderson	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *47-49,51-56,60-62 and 64-69* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47-49,51-56,60-62 and 64-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3 sheets*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' arguments, filed 10/10/2006, have been fully considered and are persuasive to overcome the rejections set forth in the Non-Final Office Action mailed 7/6/2006. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. However, upon further consideration the following rejections and/or objections are newly applied. They constitute the complete set presently being applied to the instant application. In light of the new rejections being applied against the instant claims this Office Action is **Non-Final**.

Status of the Claims

Claims 47-49, 51-56, 60-62 and 64-69 are currently pending and are the subject of this Office Action. Claims 47, 51, 53, 56, 60, 62, 64, 66 and 69 are presently amended.

Priority

The instant application is a divisional of U.S. Application No. 09/827,428 filed April 6, 2001, which is a continuation-in-part of U.S. Application No. 09/599,487, filed June 23, 2000, which claims priority from U.S. Provisional Application No. 60/141,563, filed June 29, 1999.

The instantly claimed methods are not entitled to the priority date of U.S. Provisional Application No. 60/141,563 or to the benefit of the U.S. Application No. 09/599,487 filing date. Neither application provides adequate written description or enablement for the instantly claimed methods and compounds. For example, the '563 and '487 applications are drawn to screening methods for identifying compounds that can effect P-protein function.

Support and enablement for the instant claims was found in U.S. Application No. 09/827,428. As such, the earliest effective U.S. filing date afforded the instantly claimed methods has been determined to be April 6, 2001.

Claim Rejections - 35 USC § 112 (1st Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 47-49, 51-56, 60-62 and 64-69 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is an Enablement rejection.

Applicants' specification lacks enablement of altering late endosomal/lysosomal trafficking. The instant specification fails to provide guidance that would allow the skilled artisan to practice the instant invention without resorting to undue experimentation. To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fd. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a

reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) The breadth of the claims.

While all of these *Wands* factors are considered, a sufficient *prima facie* case for lack of enablement is discussed below.

Claims 47 and 60 recite the limitation wherein the "effective amount" of the claimed compounds is an amount, which "effects an alteration in late endosomal/lysosomal trafficking". The specification discloses an assay using skin cells that tests skin cell pigmentation reduction, however assaying the effect of the claimed compounds on the "alteration in late

endosomal/lysosomal trafficking" is not described. Thus, although applicants have assessed the effect of compounds on pigmentation, they have not demonstrated results that indicate a direct connection between pigmentation and an alteration in late endosomal/lysosomal trafficking nor have they described a way of assaying such trafficking.

Absent a reasonable *a priori* expectation of success for assaying the effect of the claimed compounds on the alteration in late endosomal/lysosomal trafficking, an undue amount of experimentation would be required to practice the invention. For example, the skilled artisan would be required to determine the "effective amount" of each claimed compound that is sufficient to have an effect on endosomal/lysosomal trafficking with no direction or guidance from the instant disclosure.

Claim Rejections - 35 USC § 112 (2nd Paragraph)

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 47-49, 51-56, 60-62 and 64-69 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 47 and 60 recite the limitation "effects an alteration in late endosomal/lysosomal trafficking." It is unclear as to what effect is taking place, *i.e.*, what effect the compounds have on altering late endosomal/lysosomal trafficking, such as an increase or decrease in the rate, an increase or decrease in the amount being trafficked, etc. Also, it is unclear as to what is being trafficked, from where it is being trafficked, and to where it is being trafficked.

In addition, the term "late" regarding endosomal/lysosomal trafficking is also indefinite. "Late" is a relative term and it is unclear as to when such trafficking would be considered late as opposed to earlier trafficking. Applicants have failed to provide any specific definition for this term in the present specification. Lacking a clear meaning of the term "late endosomal/lysosomal trafficking," the skilled artisan would not be reasonably apprised of the metes and bounds of the subject matter for which Applicant seeks patent protection.

Claims 56 and 69 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims recite compounds of formula (III) that contain a carbon atom with five bonds. Carbon atoms cannot have five bonds.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 47, 55, 60 and 68 are rejected under 35 U.S.C. § 102(b) as being anticipated by Herstein (U.S. Patent No. 5,616,332; Issued Apr. 1, 1997) (newly cited art).

The instant claims recite a method of decreasing melanin production in a melanocyte (claims 47 and 55) and a method of reducing skin pigmentation (claims 60 and 68) comprising

administering an effective amount of sphingosine. It is noted that both methods would ideally call for topical administration of sphingosine.

Herstein teaches a cosmetic skin-renewal composition comprising sphingosine (Abstract). The topical administration of sphingosine is taught to reduce long-term irritation induced by topical application of skin-renewal stimulating acids to the skin (col. 2, lines 10-13). The preparations taught in Herstein can be used on any skin area and can be helpful in alleviating problems of wrinkles, sun damage and cracking with some effect on age spots (col. 18, lines 63-67). Claim 1 of the Herstein patent recites a method comprising administering a sphingosine-containing composition that is applied by topical application daily. The reference thus teaches the topical application of a sphingosine-containing composition. As such, decreasing melanin production in a melanocyte and reducing skin pigmentation would inherently result from said topical application.

It is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter, which there is reason to believe inherently includes functions that are newly cited, or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter to be shown in the prior art does not possess the characteristic relied on" (205 USPQ 594, second column, first full paragraph). There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003); see also *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) ("[T]he fact that a characteristic is

a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention").

In the instant case, the topical application of sphingosine will necessarily result in decreasing melanin production in a melanocyte and reducing skin pigmentation.

Claims 47, 49, 51-52, 60, 62 and 64-65 are rejected under 35 U.S.C. § 102(b) as being anticipated by Lee (U.S. Patent No. 5,569,678; Issued Oct. 29, 1996) (newly cited art).

The instant claims recite a method of decreasing melanin production in a melanocyte (claims 47, 49 and 51-52) and a method of reducing skin pigmentation (claims 60, 62 and 64-65) comprising administering an effective amount of a phenothiazine. It is noted that both methods would ideally call for topical administration of a phenothiazine.

Lee teaches a method of controlling wound scar production by administering a calcium antagonist to the wound site (Abstract). The reference teaches that the calcium antagonist can be a calmodulin inhibitor such as trifluorperazine (col. 3, lines 41-43 and 47-49). The calcium antagonists are preferably administered by topical application to the wound site (col. 5, lines 36-39). Lee claims a method of controlling scar production comprising administering an effective amount of a calcium antagonist (claim 1), including the topical administration of trifluoperazine (claims 5 and 6). The reference thus teaches the topical application of trifluoperazine. As such, decreasing melanin production in a melanocyte and reducing skin pigmentation would inherently result from said topical application.

It is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter, which there is reason to believe inherently includes functions that are newly cited, or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter to be shown in the prior art does not possess the characteristic relied on" (205 USPQ 594, second column, first full paragraph). There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003); see also *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention").

In the instant case, the topical application of trifluoperazine will necessarily result in decreasing melanin production in a melanocyte and reducing skin pigmentation.

Claims 47-48 and 60-61 are rejected under 35 U.S.C. § 102(b) as being anticipated by Peat (U.S. Patent No. 4,439,432; Issued Mar. 27, 1984) (newly cited art).

The instant claims recite a method of decreasing melanin production in a melanocyte (claims 47-48) and a method of reducing skin pigmentation (claims 60-61) comprising administering an effective amount of progesterone. It is noted that both methods would ideally call for topical administration of progesterone.

Peat teaches compositions and methods for the correction of progesterone deficiency comprising the transdermal, oral or suppository administration of a high concentration solution of progesterone (Abstract). Progesterone is taught to be useful in treating psoriasis, eczema, and senile skin changes including warts and superficial burns (col. 1, lines 46-56). The compositions taught in Peat can be administered by spreading on the skin (col. 2, lines 15-22). Peat claims a method of administering progesterone to a patient in need thereof comprising administering progesterone "by means other than intravenous injection" (claim 5), including topical administration (claim 7). The reference thus teaches the topical application of progesterone to a patient in need thereof. As such, decreasing melanin production in a melanocyte and reducing skin pigmentation would inherently result from said topical application.

It is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter, which there is reason to believe inherently includes functions that are newly cited, or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter to be shown in the prior art does not possess the characteristic relied on" (205 USPQ 594, second column, first full paragraph). There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003); see also *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and

enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention").

In the instant case, the topical application of progesterone will necessarily result in decreasing melanin production in a melanocyte and reducing skin pigmentation.

Claims 47 and 60 are rejected under 35 U.S.C. § 102(b) as being anticipated by Hashizume *et al.* (CA 126:190762) (cited by applicant).

The instant claims recite a method of decreasing melanin production in a melanocyte (claims 47) and a method of reducing skin pigmentation (claims 60) comprising administering an effective amount of a compound of Formula (I). It is noted that both methods would ideally call for topical administration of a compound of Formula (I).

Hashizume *et al.* teach melanin formation inhibitors containing pregnenolones (Abstract). The reference teaches that pregnenolone showed "significant whitening effect on cultured HM3KO cells (human skin melanoma cells) (*id.*). Formulation examples include ointments, skin lotions, and cosmetic packs (*id.*). The reference thus teaches the topical application of a compound of Formula (I), *i.e.*, wherein X is O, R_1 is $-C(O)(C_1\text{-}C_6)$alkyl, R_2 is Me, R_3 is Me and R_4 is –C(O)Me. As such, decreasing melanin production in a melanocyte and reducing skin pigmentation would inherently result from said topical application.

It is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter, which there is reason to believe inherently includes functions that are newly cited, or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter

to be shown in the prior art does not possess the characteristic relied on" (205 USPQ 594, second column, first full paragraph). There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003); see also *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention").

In the instant case, the topical application of the pregnenolones taught in Hashizume *et al.* will necessarily result in decreasing melanin production in a melanocyte and reducing skin pigmentation.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

James D. Anderson, Ph.D.
Patent Examiner
AU 1614

January 8, 2007

PHYLLIS SPIVACK
PRIMARY EXAMINER